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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	**PAPER NUMBER**
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/612,179	KREUTZER ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,6-9,16 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,6-9,16 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims depend from claims 4 or 8 and recite that the separate RNA strands are chemically linked and are indefinite because claim 4 explicitly states the RNA strands are non-linked.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4 and 6-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims are directed to isolated oligoribonucleotide having a double stranded structure (dsRNA) consisting of two separate non-linked complementary RNA strands, wherein the dsRNA is 21 nucleotides in length. The specification discloses on page 4 that the dsRNA of the instant invention has 10 to 1,000, preferably 15 to 49, base pairs. The specification further discloses in example 2 a RNA of 21 nucleotides that is linked to its complement by an alkyl linker that forms a disulfide bond. The specification does not contemplate a limitation wherein the dsRNA is 21 nucleotides in length and consists of separate non-linked strands and hence does not provide support for such. Furthermore, the claims of the instant application, as originally filed, were drawn to a composition comprising an oligoribonucleotide having a double stranded structure (dsRNA) wherein the dsRNA is 10-1000 nucleotides in length. Therefore, the claim limitation of "non-linked strands" first introduced in the amendment to the claims filed April 22, 2005, constitutes new matter.

Applicants' remarks filed April 22, 2005 state that support for the amendments to the claims can be found throughout the specification, such as at page 4. A review of the specification, and particularly page 4, does not reveal support for where the various claim amendments are found. While the working examples do disclose use of a single 21 nucleotide RNA, the strands of this RNA are connected by a non-nucleotide linker, therefore RNA of the recited length appears only in the context of covalently linked strands. Applicants further state in the remarks of 4/22/05 that use of an internal example within a disclosed and claimed range to set a new bound for the claimed range

is acceptable based on the decision *In re Wertheim*, (541 F.2d 257,262, 191 USPQ 90, 96 (CCPA 1976)).

However, *Wertheim* also discusses an important issue relevant to the instant claims; whether the narrower range constitutes a different invention. The court stated on page 98, "[w]here it is clear, for instance, that the broad described range pertains to a different invention then the narrower (and subsumed) claimed range, then the broader range does not describe the narrower range."

As is well known in the art and as first disclosed by Elbashir et al. (Nature 2001, of record), the discovery that 21 and 22 nucleotide duplexes are capable of specific gene inhibition without the corresponding widespread and nonspecific degradation of mRNA represents a quantum leap forward in understanding how the RNAi process operates:

> "RNA interference (RNAi) is the process of sequence- specific, post-transcriptional gene silencing in animals and plants, initiated by double-stranded RNA (dsRNA) that is homologous in sequence to the silenced gene. The mediators of sequence- specific messenger RNA degradation are 21- and 22-nucleotide small interfering RNAs (siRNA's) generated by ribonuclease III cleavage from longer dsRNAs. Here we show that 21-nucleotide siRNA duplexes specifically suppress expression of endogenous and heterologous genes in different mammalian cell lines, including human embryonic kidney and stem cells. **Therefore, 21-nucleotide siRNA duplexes provide a new tool for studying gene function in mammalian cells and may eventually be used as gene- specific therapeutics**. (emphasis added).

Based upon this discovery, the disclosure that 21 nucleotide long dsRNAs show promise as therapeutics has stimulated an entire industry devoted to honing siRNA-mediated sequence specific gene inhibitory therapeutics. As applicants are no doubt aware, dsRNA of greater than 30 nucleotides operate differently from those having a length of 21 nucleotides. From the bottom of page 494 bridging to page 495 of Elbashir:

> "But it is known that dsRNA in the cytoplasm of mammalian cells can trigger profound physiological reactions that lead to the induction of interferon synthesis. In the interferon response, **dsRNA> 30 bp binds and activates the protein kinase PKR and 2', 5'- oligoadenylate synthetase (2', 5' -AS)**. Activated PKR stalls

translation by phosphorylated and of the translation initiation factors eIF-2a and activated 2', 5'-AS causes a marked mRNA degradation by 2', 5'-oligoadenylate-activated ribonuclease L. These responses are intrinsically sequence nonspecific to the inducing dsRNA."

Because it was well-known in the art that the use of dsRNAs longer than 30 nucleotides institutes widespread and nonspecific degradation of mRNA and are thus not desirable candidates for such therapeutics, the amendment to narrow the claimed range of dsRNA from 15 to 49 nucleotides to the presently recited 21 seeks to exclude only those RNAs responsible for the widespread and nonspecific degradation of mRNA and is considered to pertain to a different invention than originally claimed range.

Response to Arguments

Applicants traverse the new matter rejection by arguing both the parent 371 application 09/889,802 and the instant application disclose methods of making dsRNA of 15-49 nucleotides using separate and linked strands and assert these applications have written description support under 35 U.S.C. § 112 for making dsRNA that specifically inhibits the expression of a target gene by synthetically preparing two separate strands of RNA and then hybridizing them to form a dsRNA that can be 15-49 base pairs, citing page 4 of the specification. This argument is not persuasive because the existence of support for RNA of 15-49 nucleotides is not at issue; the issue is whether RNA of 21 nucleotides constitutes a different invention from that originally claimed.

Applicants further argue the parent application discloses an example within the originally cited claim range and they are entitled to use a value presented in an example

as a replacement for a previously recited range that includes this value. This concept of using an exemplified value within a range as an endpoint for a new range is based on the finding in *In re Wertheim* and, as described in the rejection of record, this is acceptable so long as the narrower range does not constitute a different invention. The narrower range is considered to be a different invention for the reasons set forth above.

Applicants have characterized the rejection as a requirement by the examiner stating that a linker must be present in any claim that relies on example 2 as a basis for amendment. The rejection is based solely on whether the specification provides support for the invention as claimed and no such requirement has been made.

Applicants argue the presently pending claim range of 15-21 nucleotides solves the same problem as the original range 15-49 nucleotides, noting that page 3 of the specification teaches that dsRNA with a length of over 50 nucleotide pairs induces cellular mechanisms in mammalian and human cells such as the dsRNA-dependent protein kinase or the 2-5A system and that the present invention overcomes this disadvantage in particular. Applicants assert an "after the invention" reference shows that less than 30 nucleotides is preferred and further asserts that the examiner has incorrectly attributed a finding to Elbashir, noting that the instant specification teaches that inhibition of the RNAi effect can be reduced by decreasing the size of the dsRNA used, an effect that appears at less than 49 nucleotides and continues to 15 nucleotides.

The teaching that RNA of less than 30 base pairs is preferred is not found in post-filing art. While the page of the specification cited by applicants states RNA of less

than 50 base pairs avoids the cellular response, prior art from well before the filing date teaches that avoidance of these responses actually requires RNA of less than 30, not 50, base pairs. For example, Manche et al. (Molecular and Cellular Biology 1992) analyze the structural requirements for activation of the protein kinase DAI, the double-stranded RNA-activated inhibitor of translation. Manche et al. teach that molecules shorter than 30 base pairs fail to bind stably and do not activate the enzyme, while molecules longer than 30 base pairs bind and activate the enzyme with an efficiency that increases with increasing chain length, reaching a maximum at about 85 base pairs. Additionally, Minks et al. (Journal of Biological Chemistry 1979) teach that enzymes activated by long dsRNA, including protein kinase and 2'-5' oligo(A) polymerase, could not be activated by dsRNA containing poly(C) shorter than 30 nucleotides. Based on these teachings of the prior art and the teachings of Elbashir et al. of the critical importance of using dsRNA of 21-23 base pairs for gene silencing in mammalian cells, one of skill would recognize that dsRNA of 15-21 nucleotides is a different invention than that described at page 3 of the specification, which does not recognize the critical importance of the RNAs in the shorter end of the range for avoidance of the undesired cellular response.

Applicants assert that the instant specification, not Elbashir, teaches that inhibition of the RNAi effect appears at less than 49 nucleotides and continues to 15 nucleotides. This argument is not persuasive because the instant specification fails to recognize the critical importance of 21 nucleotide RNAs in avoiding cellular response as compared to RNAs of more than 30 base pairs. In fact, the sole discussion of the result

of gene inhibition by a 21 nucleotide dsRNA in the specification refers not to any significance of the length, but to the fact that the 21mer RNA was not two separate strands; page 19 states that "even shorter dsRNAs can be used for specifically inhibiting gene expression in mammals when the double strands are stabilized by chemically linking the single strands."

Claim Rejections - 35 USC § 102

The instant invention is drawn to an isolated oligoribonucleotide consisting of two separate non-linked RNA strands of 21 nucleotides wherein the first strand is complementary to a mammalian target and the second strand is complementary to the first strand. In specific embodiments, the target gene is a mammalian gene, one strand of the dsRNA is fully complementary to the target gene, the two RNA strands are fully complementary to each other and the target is a primary or processed RNA transcript.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows: The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The instant application does not receive the benefit of 09/889,802 or earlier applications because claims 4 and 6-9 of the instant application are not supported by the specification and claims of these applications, as demonstrated in the new matter rejection above. The parent applications do not disclose a limitation wherein the dsRNA contains separate non-linked strands and is 21 nucleotides in length. Thus, the effective filing date is determined to be that of the instant application, July 2, 2003.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 4 and 6-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Elbashir et al. (Nature 2001, of record).

Elbashir et al. disclose 21-nucleotide siRNA duplexes that are transfected into mammalian cells to specifically suppress expression of endogenous and heterologous genes in different mammalian cell lines (see page 494). Elbashir et al. also disclose duplexes comprising deoxythymidine, which is a modified ribonucleotide to enhance nuclease resistance (see pages 495 and 496).

Thus, Elbashir et al. disclose all limitations of and anticipate claims 4 and 6-9.

Claims 4 and 6-9 are rejected under 35 U.S.C. 102(e) as being anticipated by Tuschl et al. (WO 02/44321, of record).

Tuschl et al. disclose dsRNA consisting of two separate RNA strands of 19-25 nucleotides, preferably 21 nucleotides, that are capable of mediating RNAi, including in mammalian cells (see pages 3-4 and page 8, lines 4-25). One strand of the duplex is preferably 100% complementary to the target and siRNAs containing at least one modified nucleotide analog, for example a 2'-O-methyl sugar modification of a phosphorothioate are especially preferred (see pages 6 and 46). Tuschl et al. also disclose (see page 44) that the dsRNA of their invention can be 21 nucleotide siRNA duplexes with blunt ends, which are two strands fully complementary to each other.

Therefore, Tuschl et al. disclose all limitations of and anticipate claims 26-33 and 35.

Response to Arguments

Applicants traverse the art rejections of record by noting these references are not available as prior art. These arguments are not persuasive because the priority date of the instant application remains July 2, 2003.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance.

Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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Tracy Vivlemore
Examiner
Art Unit 1635

TV
October 4, 2007